Supplemental Material

Berkeley Madonna code

The code (given below) is based on the works by Diamond, Choudhury, Khoury and others (Choudhury et al 2001; Diamond et al. 2003, Khoury and Diamond 2003), who essentially combined the Kjellström and Nordberg cadmium model (Kjellström and Nordberg 1978; Kjellström and Nordberg 1985) with a model for lead biokinetics (Leggett 1993; Pounds and Leggett, 1998). The eight-compartment model was implemented in the Berkeley Madonna (version 8.3) software.

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STARTTIME = 0
STOPTIME=365*80
DT = 1
DY = 365
DTOUT = 365/12        ;print result monthly
YEARS = TIME/DY   ;conversion from days to  years
                      ;units are L for volume, kg for weight (i.e. density=1), days for time, µg for
cadmium amount, µg/g creatinine for urinary excretion

;-----------------------------------------GROWTH------------------------------------------------------
W = Wb + Wc*YEARS/(H+YEARS) + Wa/(1+K*EXP(-L*Wa*YEARS))          ;growth
curve

Wb = 3.5          ;weight at birth
Wc = 22           ;weight of child at max growth rate, 22 kg for females, 23 kg for males
Wa = 3            ;weight at adulthood, 34 kg for females, 50 kg for males
H = 3             ;age when weight is half Wc
K = 600           ;empirically fit logistic constant
L = 0.017         ;idem, 0.017 for females, 0.0095 for males

Wbl = VCbl*W          ;blood mass (kg)
Wrbc = VCrbc*Wbl   ;red blood cells (kg)
Wki = VCki*(Wa+Wb+Wc)*(W/(Wa+Wb+Wc))^0.85        ;kidney mass (kg)
Wli = VCli*(Wa+Wb+Wc)*(W/(Wa+Wb+Wc))^0.85         ;liver mass (kg)

VCbl = 0.067
VCrbc = 0.42

VCki = 0.0045
VCli = 0.025

LBM = W*VClbm      ;lean body mass
VClbm = 0.85            ;0.85 for females, 0.88 for males
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CRur = (LBM/0.0272 - 8.58) / 1000 ;creatinine excretion (g/day)

;-------------------------------------ORAL ABSORPTION---
WKDOSE = 1.5 ;weekly intake (µg/kg bw/wk)
INGEST = WKDOSE/7*W ;daily intake (µg/day)
AF1 = 0.1 ;fraction available for absorption, e.g. 0.1 for females, 0.05 for males

YSTMC' = INGEST - AGSCAL*RSTMC*YSTMC ;change in amount of Cadmium in stomach (µg/day)
INIT YSTMC = 0 ;initial amount of Cadmium in stomach at birth (µg)
RSTMC = 24 ;basal rate of stomach emptying (day-1)

AGSCAL = GRAPH (YEARS) (0,1.66667) (10,1.66667) (15,1.33333) (90,1)
;age adjustment of stomach emptying rate

YSIC' = AGSCAL*RSTMC*YSTMC + H1TOSI*RLVR1*YLVR1 + TOFECE*CF*RPLS*YPLS - AGSCAL*RSIC*YSIC ;change in amount of Cadmium in small intestine (µg/day)
INIT YSIC = 0 ;initial amount of Cadmium in small intestineat birth (µg)
RSIC = 6 ;transfer rate (day-1)

YULI' = AGSCAL*(1-AF1)*RSIC*YSIC - AGSCAL*RULI*YULI ;change in amount of Cadmium in upper large intestine (µg/day)
INIT YULI = 0 ;initial amount of Cadmium in upper large intestineat birth (µg)
RULI = 1.85 ;transfer rate (day-1), taken from AALM

YLLI' = AGSCAL*(1-AF1)*RULI*YULI - AGSCAL*RLLI*YLLI ;change in amount of Cadmium in lower large intestine (µg/day)
INIT YLLI = 0 ;initial amount of Cadmium in lower large intestineat birth (µg)
RLLI = 1 ;transfer rate (day-1)

;----------------------------RED BLOOD CELL COMPARTMENT-----------------------------------
YRBC' = RBCin - ARRBC*YRBC ;change in Cadmium in red blood cells (µg/day)
RBCin = YPLS*RPLS*TORBC*CFRBC ;transfer from plasma to red blood cells (µg/day)
RPLS = RPLAS*TOSUM
RPLAS = 2000 ;default value (day-1)
TOSUM = TORBC + TOEVF + TOPROT + TOURIN + TOFECE + TOLVR1 + TOKDN1 + TOKDN2 + TOSOF1
TORBC = 0.05 ;fraction transferred to red blood cells
CFRBC = IF RBCONC<RBCNL THEN TORBC ELSE TORBC*(1-(RBCONC-RBCNL)/(SATRAT-RBCNL))^POWER ;saturable correction factor

RBCNL = 60 ;µg/dL
SATRAT = 350 ;µg/dL
POWER = 1.5 ;unitless
INIT YRBC = 0 ;initialamount of Cadmium at birth (µg)
RBCONC = YRBC/Wrbc ;Cadmium concentration in red blood cells
;--------------------------------EXTRAVASCULAR FLUID COMPARTMENT--------------------

EVFin = YPLS*RPLS*TOEVF*CF ;transfer from plasma to extravascular fluid (µg/d)
TOEVF = 0.5 ;fraction transferred to extravascular fluid
CF = (1-TORBC*CFRBC)/(1-TORBC) ;correction factor
YEVF' = YPLS*RPLS*TOEVF*CF - REVF*YEVF ;change in amount of Cadmium in extravascular fluid (µg/d)
INIT YEVF = 0 ;initial amount of Cadmium at birth (µg)
REVF = TOEVF*RPLS/SIZEVF
SIZEVF = 3

;-----------------------------------PLASMA PROTEIN COMPARTMENT---------------------------
YPROT' = YPLS*RPLS*TOPROT*CF - RPROT*YPROT ;change in plasma protein bound Cadmium (µg/d)
INIT YPROT = 0 ;initial amount of Cadmium at birth (µg)
TOPROT = 0.0002 ;fraction transferred to bound plasma
RPROT = 0.07 ;rate constant from bound protein

;-----------------------------------BLADDER COMPARTMENT--------------------------------------
URINin = YPLS*RPLS*TOURIN*CF ;transfer from plasma to bladder (µg/d)
TOURIN = 0.000026 ;fraction transferred to bladder

;-------------------------------------FECAL COMPARTMENT---
FECEin = YPLS*RPLS*TOFECE*CF ;transfer from plasma to small intestine (µg/d)
TOFECE = 0.000055 ;fraction transferred to small intestine

;--------------------------------OTHER SOFT TISSUES COMPARTMENT ------------------------
YSOF1' = YPLS*RPLS*TOSOF1*CF - RSOF1*YSOF1 ;change in amount of Cadmium in extravascular fluid (µg/d)
TOSOF1 = 0.000022 ;fraction transferred to red blood cells
INIT YSOF1 = 0 ;initial amount of Cadmium at birth (µg)
RSOF1 = 0.00014 ;rate constant from other soft tissues

;----------------------------------PLASMA COMPARTMENT--
YPLS' = PLSin - PLSout ;change in Cadmium in plasma (µg/d)
PLSin = RPROT*YPROT + ARRBC*YRBC + REVF*YEVF + RSOF1*YSOF1 + H1TOBL*RLVR1*YLVR1 + ARKDN2*YKDN2 + AF1*AGSCAL*RSIC*YSIC
;transfer from all other compartments to plasma (µg/day)

PLSout = YPLS*RPLS*TORBC*CFRBC + YPLS*RPLS*TOEVF*CF + YPLS*RPLS*TOPROT*CF + URINin + FECEin + YPLS*RPLS*TOLVR1*CF + YPLS*RPLS*TOKDN1*CF + YPLS*RPLS*TOKDN2*CF + YPLS*RPLS*TOSOF1*CF
;transfer from plasma to all other compartments
INIT YPLS = 0 ;initial amount of Cadmium in plasma at birth (µg)

ARRBC = GRAPH (YEARS) (0,0.461) (1,0.462) (5,0.277) (10,0.139) (90,0.139)
ARKDN2 = GRAPH (YEARS) (0,0.00006) (25,0.00006) (30, 0.00008) (40,0.00012) (60,0.00018) (90,0.00018)
;transfer rate constant from "other" kidney tissue to kidney tissue associated with urinary excretion

;-----------------------------------LIVER COMPARTMENT ----------------------------------
YLVR1' = YPLS*RPLS*TOLVR1*CF - YLVR1*RLVR1*(H1TOBL+H1TOSI)
;change in Cadmium in liver (µg/d)
TOLVR1 = 0.094 ;fraction transferred to liver
INIT YLVR1 = 0 ;initial amount of Cadmium in liver at birth (µg)
RLVR1 = 0.00014 ;rate constant from liver
H1TOBL = 0.4 ;fraction going to plasma
H1TOSI = 0.6 ;fraction going to small intestine

;-------------------------KIDNEY URINARY PATHWAY COMPARTMENT -----------
YKDN1' = YPLS*RPLS*TOKDN1*CF - YKDN1*RKDN1 ;change in Cadmium in kidney (µg/d)
TOKDN1 = 0.000022 ;fraction transferred to kidney - urinary pathway
INIT YKDN1 = 0 ;initial amount of Cadmium in kidney at birth (µg)
RKDN1 = 1 ;default value for all ages

;--------------------------OTHER KIDNEY TISSUE COMPARTMENT ------------------
YKDN2' = YPLS*RPLS*TOKDN2*CF - YKDN2*(RKDN2 + ARKDN2) ; RKDN2 represents the rate coefficient for transfer from the OTHER KIDNEY compartment to PLASMA;
TOKDN2 = 0.13 ;fraction transferred to other kidney tissues
INIT YKDN2 = 0 ;initial amount of Cadmium in kidney at birth (µg)
RKDN2 = 0.00001 ;rate constant from other kidney tissue

;-----------------------------BLADDER COMPARTMENT --------------------------------
;YBLAD' = YKDN1*RKDN1 + TOURIN*RPLS*YPLS*CFBLAD - YBLAD*ARBLAD
;change in Cadmium in bladder (µg/day)
YBLAD' = YKDN1*RKDN1 + TOURIN*RPLS*YPLS*CF - YBLAD*ARBLAD
;CFBLAD=CF
INIT YBLAD = 0 ;initial amount of Cadmium in bladder at birth (µg)

ARBLAD = GRAPH (YEARS) (0,12) (0.274,12) (1,15) (5,11) (10,8) (15,7) (90,7)
;transfer rate constant rate from bladder to urine
UEX = YBLAD*ARBLAD ;excretion in urine (µg/d)
UEXCR = UEX/CRUr ;excretion in urine (µg/g creatinine)
KIDNEY = (YKDN1+YKDN2)/Wki/1000 ;average concentration in kidney (µg/g)

References

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